

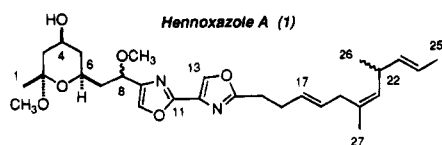
Total Synthesis of the Enantiomer of the Antiviral Marine Natural Product Hennoxazole A

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Received September 13, 1994

A large number of extracts from marine organisms show moderate to high activity in antiviral screening essays and might therefore prove useful as a source of unconventional lead structures in the development of effective drugs against viral diseases.¹ Hennoxazole A (**1**) was isolated by Ichiba et al.² from a marine sponge, a *Polyfibrospongia* sp. (phylum Porifera), and was shown to be highly active against herpes simplex virus (HSV-1, IC₅₀ = 0.6 µg/mL). This structurally diverse natural

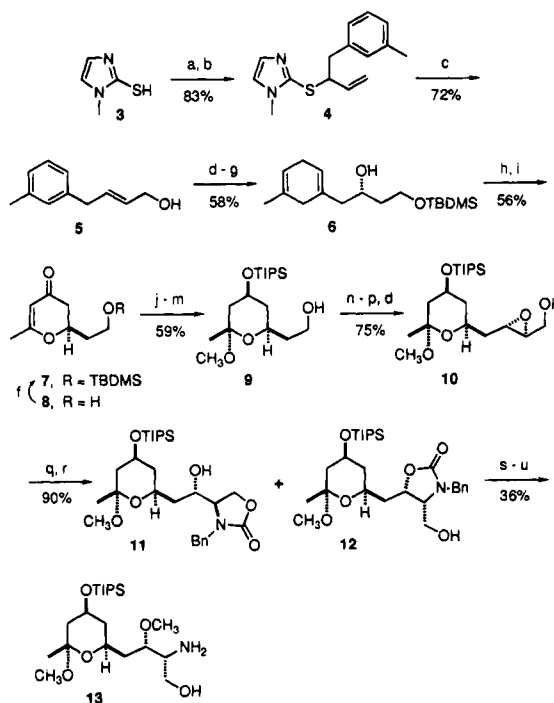


product incorporates a bisoxazole, a pyranoid glycoside, and a skipped triene unit. The relative configuration at C(2), C(4), and C(6) was determined by NMR experiments;² the absolute configuration as well as the stereochemistry at C(8) and C(22) remain unresolved.

As a part of our program for the synthesis and study of marine natural products,³ we have recently embarked on the total synthesis and structure elucidation of hennoxazole A. In this communication, we report the preparation of the (2*S*,4*S*,6*S*,8*S*,22*R*)-isomer **2**. Key features of our synthesis are (1) a highly convergent strategy that combines pyran and triene segments via a novel bisoxazole synthesis; (2) the use of a *m*-xylene as a pyran synthon; (3) a vinyl cuprate S_N2 displacement of a sterically hindered allylic ester at C(22).⁴

For the synthesis of the left side (C(1)–C(10)) segment of hennoxazole A, an Evans–Mislow rearrangement⁵ of the *S*-oxide of thioether **4** provided the (*E*)-allylic alcohol **5**⁶ in >96% diastereomeric purity (Scheme 1). Sharpless asymmetric epoxidation⁷ followed by oxirane reduction with Red-Al⁸ introduced the secondary alcohol function at C(6) that was used as a linchpin for the construction of the pyran stereocenters at C(2) and C(4). Selective silylation of the primary alcohol and dissolving metal reduction yielded the diene **6** in seven steps and 35% overall yield from commercially available mercaptoimidazole (**3**). Ozonolysis followed by reductive workup completed the unraveling of the β-diketone functionality from the meta-substituted xylene.⁹ After treatment of the complex mixture of keto-enol as well as cyclic isomers of the intermediate 6-hydroxy-8-silyloxy-2,4-octanedione with *p*-TsOH in THF,

Scheme 1^a



^a (a) Allyl bromide, 6 M NaOH, CH₂Cl₂, BnNEt₃Cl, 35 °C. (b) *n*-BuLi, α-bromo-*m*-xylene, THF, −78 °C to 20 °C. (c) MCPBA, MeOH, −30 °C to 20 °C; then Et₃NH, 20 °C. (d) *tert*-Butyl hydroperoxide, L-(+)-diisopropyl tartrate, Ti(O-*i*-Pr)₄, 4 Å MS, −20 °C. (e) Red-Al, THF, −15 °C. (f) TBDMS-Cl, Im, CH₂Cl₂. (g) Li, NH₃, *tert*-amyl alcohol, THF, −40 °C. (h) O₃, EtOAc, −78 °C; then H₂, Pd(OH)₂, 20 °C. (i) TsOH, THF, 20 °C. (j) NaBH₄, CeCl₃, THF/MeOH, −20 °C. (k) TIPSCl, Im, DMAP, DMF. (l) HC(OMe)₃, MeOH, PPTs, benzene, 20 °C. (m) LiOH, dioxane/EtOH/H₂O, 90 °C. (n) TPAP, NMO, 4 Å MS, CH₂Cl₂, 20 °C. (o) (EtO)₂P(O)CH₂CO₂Et, NaH, THF, 0 °C. (p) DIBALH, THF, 0 °C. (q) BnNCO, Et₃N, CH₂Cl₂, 20 °C. (r) NaH, THF, 0 °C to 20 °C. (s) NaH, MeI, Ag₂O, THF, 0 °C to 20 °C. (t) LiOH, dioxane/EtOH/H₂O, 80 °C. (u) H₂, Pd(OH)₂, MeOH, 20 °C.

56% of a 1:2 mixture of pyranones **7** and **8** was isolated. Reprotection of the primary alcohol function with TBDMS-Cl converted **8** back to the desired silyl ether **7**. 1,2-Reduction of the enone with NaBH₄ in the presence of CeCl₃¹⁰ occurred exclusively via axial attack, and the resulting secondary allylic alcohol was silylated with TIPS-Cl and the glycol function solvolyzed in MeOH in the presence of PPTs and methyl orthoformate to give the desired axial anomer in 71% overall yield from **7**. Selective cleavage of the primary TBDMS ether vs the secondary TIPS ether was best accomplished under strongly basic conditions with LiOH in a ternary mixture of dioxane/ethanol/water (1:1:2).

Side-chain extension of **9** to give alcohol **10** proceeded in 75% yield via oxidation with catalytic perruthenate,¹¹ Wadsworth–Emmons reaction, DIBALH reduction, and Sharpless asymmetric epoxidation. The protocol of Kishi¹² and Roush¹³ was chosen for the introduction of the amino function at C(9). Treatment of epoxy alcohol **10** with benzyl isocyanate, followed by cyclization of the intermediate urethane, resulted in a 87:13 mixture of isomeric oxazolidinones **11** and **12**. The desired major product **11** was purified by chromatography on SiO₂, *O*-methylated, hydrolyzed, and hydrogenated to give the amino

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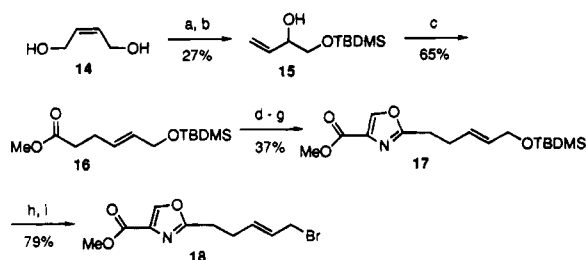
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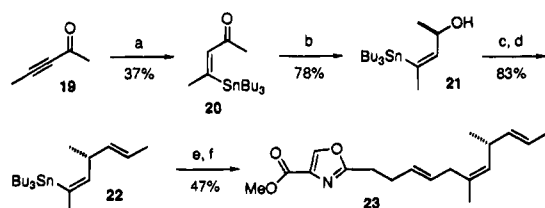
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Scheme 2^a

^a (a) HgSO_4 , H_2SO_4 , H_2O , 100 °C. (b) TBDMSCl, Im, CH_2Cl_2 . (c) MeC(OMe)_3 , $\text{C}_2\text{H}_5\text{CO}_2\text{H}$, 140 °C. (d) LiOH, MeOH/ H_2O , 20 °C. (e) Serine-OMe, *i*-BuOC(O)Cl, NEt_3 , CH_2Cl_2 , -15 °C to 0 °C. (f) Burgess reagent, THF, 70 °C. (g) CuBr_2 , DBU, HMTA, CH_2Cl_2 , 20 °C. (h) TBAF, THF, 20 °C. (i) NBS, Ph_3P , CH_2Cl_2 , -30 °C to 0 °C.

Scheme 3^a

^a (a) $[(\text{PhS})\text{Bu}_3\text{SnCu}]\text{Li}$, THF, -50 °C. (b) (*S*)-Oxazaborolidine, catecholborane, toluene, -30 °C to -20 °C. (c) 2,4,6-Trimethylbenzoyl chloride, 2,6-lutidine, CH_2Cl_2 , 20 °C. (d) $[(E)\text{-MeC=C}]_2\text{CuLi}$, THF, -20 °C. (e) I_2 , CH_2Cl_2 , 20 °C. (f) (i) *t*-BuLi, THF, -78 °C to 20 °C; (ii) ZnCl_2 , -78 °C to 20 °C; (iii) **18**, $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$, AsPh_3 , THF, 20 °C.

alcohol **13**. Overall, the left-side segment was thus prepared in 21 steps and in 3% yield.

A Pd-catalyzed coupling between allylic bromide **18** and the zinc reagent derived from vinyl stannane **22** established an efficient access to the right-side (C(11)–C(25)) segment of hennoxazole A. Acid-catalyzed rearrangement¹⁴ of (*Z*)-butenediol (**14**) and silylation of the primary alcohol function provided allylic alcohol **15** in multigram quantities (Scheme 2).

The functionalized ester **16** was readily obtained by Claisen rearrangement¹⁵ in the presence of trimethyl orthoacetate and acid. Saponification and coupling with serine methyl ester was followed by cyclodehydration with the Burgess reagent¹⁶ to give an intermediate oxazoline that was oxidized to the oxazole with cupric bromide¹⁷ in the presence of DBU and hexamethylenetetramine. *O*-Desilylation and bromination¹⁸ of the allylic alcohol led to the π -allyl palladium precursor **18**.

Conjugate addition of the cuprate¹⁹ derived from copper(I) thiophenoxide and Bu_3SnLi to ynone **19** provided vinyl stannane **20** in 37% yield as a single geometric isomer (Scheme 3). Asymmetric reduction of **20** with 20% tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaboroleborane²⁰ in the presence of stoichiometric quantities of catecholborane²¹ gave (*R*)-allylic alcohol **21** in 85% ee and 78% chemical yield. After considerable experimentation, we found that conversion of **21** to the 2,4,6-trimethylbenzoate allowed a subsequent very clean $\text{S}_\text{N}2$ inversion with propenyl cuprate to provide the skipped diene **22** in 83% yield. Direct palladium-catalyzed coupling of the

Scheme 4^a